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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/068,916	02/11/2002	Thomas Ritter	219148US0CONT	9410

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,916	RITTER ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to an amendment filed 12/19/02. Claims 1-17 have been cancelled. Claims 18-48 are pending in this application.

Response to Amendment

Receipt of priority documents is acknowledged establishing June 9, 2000 as the effective priority date of this application.

Claim Objections

Claim 35, 37, 38, 39, 40 and 41 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 35, 37, 39, 40 and 41 recite that the therapeutic gene is **transferred** into a graft recipient cell and they depend from claim 30 which recites that the immunomodulatory gene is **transfected** into graft recipient-specific T cells. Transferring genes into a cell can include the method of transfecting and therefore transferred is a more broad term than transfected. **This is a new rejection precipitated by applicant's amendment.**

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Georges et al. Georges et al. teach generation of in vitro modified T cells which are stimulated and contain a

therapeutically used gene- the herpes simplex virus thymidine kinase gene. Recipient-specific T cells (cytotoxic T-lymphocytes) were stimulated with allogeneic irradiated peripheral blood mononuclear cells (page 540 column 1 to last sentence through 541, column 2, line 1-2) and retrovirally transduced with HSVTK, a gene often used therapeutically (page 540, column 2, 3rd paragraph). Opposite evidence to the contrary, the product of Georges et al. is not patentably distinct from the invention of the instant application. The patentability of the instant invention, which while defined by the process, is based upon the product (see MPEP 2113). **This rejection is necessitated by applicant's amendment.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

For reasons of record in the first office action and also further discussed below, the rejection of claims under 35 U.S.C., first paragraph, are maintained. The portion of the rejection that refers to use of the *in vitro* gene modified T cell for **prevention** of an allogeneic graft rejection is withdrawn in light of amendment to claims which drop this language.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 23-27 and 35-41 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 and 25 are vague and unclear in that it recites that the *in vitro* T cell is produced by the isolation of a lymphocyte that is an irradiated T cell, an irradiated cell which expresses a dominant MHC molecule, or a recipient T cell. While these cells are isolated as part of the inventive step, they do not appear to be used further in the invention. If they are the same cells as the mixed lymphocyte culture referred to further in the claim then the fact that they are referred to in different terms is confusing. **This is a new rejection precipitated by applicant's amendment.**

Claim 21 and 25 are further vague and confusing in the production steps. The steps appear to be overlapping with the process of claim 18 but it is not clear what the relationship between the two is. **This is a new rejection precipitated by applicant's amendment.**

Claim 21, 23-27 and 35-41 are vague and unclear in reciting that the therapeutic gene is transferred into the graft recipient-specific T cell by culturing or incubating a mixed lymphocyte culture with... It appears that the mixed lymphocyte culture is in fact the graft recipient-specific T cell but there is no actual connection between the two in the claim language. The connection between the graft recipient-specific T cell and the mixed lymphocyte culture should be made clear. **This is a new rejection precipitated by applicant's amendment.**

Response to Arguments

On page 6 of the amendment filed 12/19/02, applicant traverses the rejection under 35 U.S.C 102(b). Applicant argues that the invention of Georges et al. differs from that in the instant application as the TK gene mediates cell death and cannot be considered a therapeutic gene.

Applicant's arguments filed 12/19/02 have been fully considered but they are not persuasive. HSVTK does find use therapeutically. As reviewed in Marples et al. for example, HSVTK is used in Cancer gene therapy as a therapeutic agent. While the mechanism of HSVTK is to mediate cell death, it is commonly used as a therapeutic gene to kill cancer cells.

On pages 6-8, applicant traverses the rejections under 35 U.S.C. 112, first paragraph by reciting Dr. Ritter's Declaration of 12/19/02 as teachings that enable the skilled artisan to practice the full scope of the claimed invention. Examiners response to these arguments will be provided below in response to the declaration.

The Declaration of Dr. Ritter states that 1) vIL-10 inhibits TNFα production by human peripheral blood lymphocytes (PBMC) stimulated by lipopolysaccharide (LPS) as shown in Exhibit 1 Therefore, vIL-10 is bioactive following transfer into cells and is effective for inhibiting inflammatory responses. 2) Long term gene expression is achieved following retroviral-mediated gene transfer 3) stable tolerance is achieved as immunomodulation occurs in the early stages of transplantation 4) vIL-10 does not have the stimulatory activity of cellular IL-10 and 5) retroviral therapy has been successfully demonstrated in humans.

The Declaration and exhibits under 37 CFR 1.132 filed 12/19/02 are insufficient to overcome the rejection of claims 18-48 based upon 35 U.S.C. 112, first paragraph, as set forth in the last Office action because of the following reasons:

The instant invention does not teach methods for clinical or pre-clinical use of the proposed invention such that the instant invention can be used. Essential factors not taught include treatment intensity, accompanying immuno-suppression drugs and schedule of treatment as well as amount of retrovirus to be used. Guidance for the generation of in vitro modified T cells is provided in the specification but not for use of the invention for gene therapy. While exhibit 1 details transfer of vIL-10 transduced cells *in vitro* into isolated PBMC, no data on *in vivo* use is provided. It is unclear if the in vitro data provided by declarant would be considered by the skilled artisan as being correlated with successful treatment of patients for allogeneic graft rejection.

Details for *in vivo* gene therapy following retroviral transfer into the T cells are not adequately taught in the specification. Cavazzano-Calvo et al. teaches retroviral delivery into hematopoietic stem cells and allogeneic bone marrow transfer to treat SCID-XI in patients. Aiuti et al. teach a similar gene transfer protocol for hematopoietic stem cells and their transfer into patients. These teachings are designed to show that long-term expression can be achieved following gene transfer therapy. Any successes recited in the cited papers cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of said references. Specifically, the instant specification teaches the generation of in vitro modified graft recipient T cells from a mixed lymphocyte culture (origin unstated), bioassays for expression of therapeutic genes and *in vitro* analysis of their immuno-regulatory potential. These

teachings in no way provide the skilled artisan with the ability to use these cells to treat a patient for allogeneic graft rejection. Auiti et al. and Cavazzano-Calvo et al. teach the use of CD34+ cells harvested from specific patients. Specific treatment protocols are provided in both articles. For example, Auiti et al then teach 21% to 25% transduced colony-forming units in culture with nonmyeloablative conditioning with busulfan as well as follow up protocols and bioassays. These teachings differ from Cavazzano-Calvo et al. who teach infusion of 19x10(6) to 17 x 10(6)/kg of cells into patients without prior chemoablation as well as intravenous immunoglobin therapy. No *in vivo* protocol steps or teachings are provided for in the specification. Therefore, the teaching of the specification and prior art do not teach one how to use the *in vitro* modified T cells for therapeutic purposes as neither the specification nor the prior art provide the specific dosages to be administered to patients, the schedule of treatments, the specific modes of administration etc for the *in vitro* modified cells of the invention.

The art cited by Dr. Ritter teaches that long-term expression can be achieved. Dr. Ritter further explains that the efficiency of transplantation is not an obstacle for this therapy as the cells to be transplanted are autologous and do not induce the immune response associated with allogeneic cells. As well, it is noted that the *in vitro* expression of cytokines in the *ex vivo* transduced cells mimics that seen *in vivo*, this is but one factor to be considered for evaluating successful gene therapy protocols. As noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments. However, the

unpredictability of using the claimed invention in humans is accentuated due to the lack of methods or processes disclosed in the specification. In view of the unpredictability of the art to which the invention pertains and the lack of established animal models and clinical protocols: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description for how to reasonably determine how to use the claimed cellular compositions.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD
Examiner
Art Unit 1636

March 10, 2003

DAVID GUZO
PRIMARY EXAMINER